



Research Article

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HEART RATE VARIABILITY AS A MARKER OF CARDIAC AUTONOMIC NEUROPATHY AND AUTONOMIC DYSFUNCTION IN PREDIABETIC PATIENTS: A RETROSPECTIVE STUDY

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Abstract

Objectives: Heart rate variability has been associated with autonomic neuropathy, which is seen in diabetes. Cardiac autonomic neuropathy is found to be related to a poor prognosis in diabetic patients. It is thought that neuropathy that develops in diabetic patients begins in the early stages. We aimed to assess heart rate variability (HRV) in prediabetic patients to explore whether autonomic changes may begin during the prediabetes stage.

Materials and Methods: This retrospective study included prediabetic patients who underwent 24-hour Holter ECG monitoring. Patients were identified based on fasting plasma glucose (FPG) and HbA1c values extracted from medical records. Prediabetes was defined as HbA1c 5.7–6.4% and fasting plasma glucose 100–126 mg/dL. Patients with thyroid dysfunction, overt diabetes, arrhythmias or those using drugs affecting heart rate were excluded. HRV parameters, including SDNN, SDANN, rMSSD, pNN50, triangular index, and frequency-domain measures (LF, HF, VLF, LF/HF), were analysed.

Results: Fifty participants were included (25 prediabetic, 25 controls). The groups were similar in age and sex. All HRV parameters were lower in prediabetic patients compared to controls. Time-domain measures SDANN, rMSSD, pNN50, and triangular index and frequency-domain measures HF, VLF, and LF/HF ratio were significantly reduced ($p < 0.05$). Effect sizes and 95% confidence intervals were reported, and sensitivity analyses adjusted for age and sex confirmed findings.

Conclusion: HRV is reduced in prediabetic patients, consistent with early autonomic dysfunction. These findings suggest that cardiac autonomic neuropathy may begin in prediabetic patients. All HRV parameters were lower than those of the control group and can serve as non-invasive indicators of early autonomic dysfunction and cardiac autonomic neuropathy.

Keywords: Prediabetes, heart rate, autonomic neuropathy.

Introduction

Cardiac autonomic neuropathy has been associated with increased morbidity and mortality in diabetic patients.¹ Neuropathy in diabetic patients is thought to begin in the early stages; studies suggest that autonomic dysfunction may begin before the diagnosis of diabetes, during the prediabetic stage.¹ Heart Rate Variability Indicates Early Autonomic Dysfunction in Prediabetic Patients. Investigation of heart rate variability in prediabetic patients may indicate that autonomic neuropathic changes begin during the prediabetic phase.

Preventing the diagnosis of diabetes at the prediabetes stage is the most beneficial method to treat the complications that may arise. Macrovascular and microvascular complications of diabetes directly affect the cardiovascular system, and most of the diabetes deaths are cardiovascular-related. Early recognition may be cost-effective and guide clinicians and at-risk individuals in implementing timely lifestyle interventions. Cardiovascular autonomic neuropathy can be diagnosed noninvasively by considering the heart rate variability. Diabetic cardiovascular autonomic neuropathy, which is not studied much in clinical practice and can be diagnosed early due to clinicians paying more attention to other macrovascular complications and microvascular complications of diabetes, is diagnosed late.

The definition of 'prediabetes' has been accepted by the ADA for conditions that do not have high blood sugar to meet the diagnosis of diabetes, but are at a level that cannot be considered normal.² (Table 1)

Table 1. Criteria for diagnosing diabetes mellitus and other glucose metabolism disorders¹

	Normal	Prediabetes	Diabetes
Fasting Plasma Glucose(FPG)	<100 mg/dL	100-125 mg/dL	≥ 126 mg/dL
2-hr OGTT (75 g glucose)	<140 mg/dL	140-199 mg/dL	≥ 200 mg/dL
HbA1c	<5.7%	5.7-6.4%	≥ 6.5%
Random Plasma Glucose	-	-	≥ 200 mg/dl + symptoms

FPG: Fasting Plasma Glucose, OGTT: Oral Glucose Tolerance Test, HbA1c: Hemoglobin A1c

In the light of the new diagnostic criteria, the presence of fasting plasma glucose in the range of 100-125 mg/dL 'impaired fasting glucose [IFG]' and/or oral glucose tolerance test (OGTT 75 g) 2nd-hour value in the range of 140-199 mg/dL 'impaired glucose tolerance [IGT]' and/or HbA1c value defined as 5.7-6.4% defines the cases where both diabetes risk and complications and cardiovascular disease risk increase.³

The definition of 'prediabetes' is used for values that do not fully meet the diagnostic criteria for diabetes, but whose plasma glucose levels are higher than normal., includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT) which were previously referred to as 'Borderline Diabetes' or 'Latent Diabetes', are now accepted as 'Prediabetes'.

The risk of developing diabetes mellitus in pre-diabetic individuals increases up to 4-9% in those with IFG or IGT, and up to 19% in those with both.⁴

According to the data described in TURDEP-II, the prevalence of diabetes in our country was found to be 13.7%, the prevalence of IGT was found to be 7.9%, and the prevalence of IFG was found to be 14.7%.⁵ In the pathophysiology of the transition from prediabetes to diabetes, insulin resistance and beta-cell dysfunction are prevalent, and it is accepted that this mechanism starts at the prediabetes stage before the development of diabetes.⁶

According to research findings, prediabetes is associated with macrovascular and especially cardiovascular complications, and the cardiovascular risk is further increased in people with high plasma glucose at the second hour, and in people with IGT and IFG. ⁷ It has been revealed that fasting blood sugar, IFG, IGT and prediabetic HbA1c at prediabetic levels are directly associated with cardiovascular mortality and complications and are independent risk factors.^{8, 9, 10}

It has also been shown that complications such as nephropathy, retinopathy and neuropathy seen in diabetes can also be seen in prediabetes, and the risk of peripheral neuropathy and autonomic neuropathy is increased.¹¹

Heart rate variability refers to the time variability between beats in a normal sinus rhythm in each time period, that is, heart rate fluctuations around the mean heart rate.¹²

There are changes in heart rate related to autonomic tone due to exercise, physical and emotional stress, breathing and metabolic reasons, and it is accepted as an indicator of cardiac autonomic sympathetic and parasympathetic regulation.¹³

The continuous variation of intervals between heartbeats in people with normal sinus rhythm is physiological, and the decrease in heart rate variability indicates autonomic dysfunction.¹² Therefore, measurement of heart rate variability in Holter ECG draws attention as a non-invasive method that can be used to indirectly evaluate the autonomic nervous system.¹⁴

The first thing to look at in the measurement of heart rate variability is the analysis of successive R waves measured on the ECG. Although it is essentially a P wave that reflects the sino-atrial output, R waves that are measured more easily are preferred.¹² Different methods can be applied to detect RR intervals. After ECG records are made, heart rate variability parameters are calculated with the help of programs, abnormal early beats are removed from the record, and measurement can be accepted if at least 85% of the recorded R waves are normal R.¹⁵ Heart rate variability measurement is mostly made from the recordings obtained during Holter monitoring, normal-normal (NN) R intervals, which are measured by the program that processes the data in Holter, are taken as a basis for the measurement.¹²

Heart rate variability measurement is basically done by two methods: time measurements and frequency measurements.¹²

Time measurements: It is based on analysis of intervals between normal beats in 24-hour ECG recordings. The intervals (NN interval) between two consecutive beats coming out of the SA node are evaluated. (Table 2)

Autonomic neuropathy is a common complication of diabetes and, in practice, occurs in the form of persistent tachycardia, bladder atony, nocturnal diarrhoea, postural hypotension, excessive sweating, gastroparesis, and heart rate variability, which manifests itself with a decrease in time measurements.¹⁶

Cardiovascular autonomic neuropathy is an important complication that increases mortality, which can be found in 40% of diabetic patients. While the five-year survival rate of a patient without neuropathy is reported as 99%, this rate decreases to 60-75% in a patient with clinically significant autonomic neuropathy.¹⁷

It has been determined that the presence of autonomic neuropathy in diabetic patients is an unfavourable prognostic factor.¹⁷ For the diagnosis and follow-up of cardiac autonomic neuropathy, time-dependent heart rate variability is a noninvasive method that is more sensitive than classical cardiovascular reflex tests and is easy to repeat in practice.¹⁷

Patients with diabetes should be questioned in terms of signs and symptoms of autonomic neuropathy. Clinically unaware of autonomic neuropathy, hypoglycemia can be seen as resting tachycardia, orthostatic hypotension, decreased heart rate variability, sudden cardiac death, silent myocardial infarction, gastroparesis, faecal incontinence, constipation, diarrhoea, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction (decreased or increased sweating).

Table 2. Common heart rate variability time measures ¹²

Variable	Unit	Definition
Mean NN	ms	Cycle length between two normal beats
Day/night difference	ms	The difference in the mean NN intervals obtained during the day and night
SDNN	ms	Standard deviation of all NN intervals throughout the study
SDNN index	ms	Average of standard deviations of all NN intervals over 5 min recordings
SDANN	ms	Standard deviation of the mean NN interval over the 5-min recordings
pNN50	%	Number of adjacent NN intervals with a difference of more than 50 ms NN 50 divided by the total number of NN.
rMSSD	ms	Square root of the sum of the squares of the differences of consecutive NN

NN: Normal-to-Normal, SDNN: Standard Deviation of NN intervals, SDNN index: Standard Deviation of NN intervals index, SDANN: Standard Deviation of the Average NN intervals, NN50: Number of NN intervals differing by more than 50 ms, pNN50: Percentage of NN50 intervals, rMSSD: Root Mean Square of Successive Differences

Frequency measurements: This method separates heart rate signals according to their frequency and intensity. (Table 3)

Table 3. Heart rate variability frequency measures¹²

Parameter	Frequency (Hz)	Specifications	Recording time
HF	High-frequency band 0.15-0.40	-Related to parasympathetic activation -Affected by breathing	Short (1-5 min) and long
LF	Low-frequency band 0.04-0.15	-Reflects sympathetic and parasympathetic tone -Thermoregulation and peripheral Relates to vasomotor activity	Short (1-5 min) and long
MF	Mid-frequency band 0.05-0.20	-Reflects sympathetic and parasympathetic tone -Related to baroreceptor activity	Short (1-5 min)
VLF	Very low frequency band 0.0033-0.04	-Unknown	Short (1-5 min) and long
ULF	Ultra-low frequency band <0.0033	-Unknown	Long (>24 hours)

HF: High-Frequency band, LF: Low-Frequency band, MF: Mid-Frequency band, VLF: Very Low Frequency band, ULF: Ultra-Low Frequency band

Materials and Methods

The study was approved by the Non-Interventional Clinical Research Ethics Committee of the Faculty of Medicine, Ufuk University, with application date and number 20200703/16. This retrospective comparative study was conducted at the Ufuk University Dr. Rıdvan Ege Hospital, affiliated with the Faculty of Medicine at Ufuk University. Prediabetic Patients and age- and sex-matched controls who presented to the cardiology outpatient clinic between January 2018 and January 2020. and underwent Holter ECG monitoring were screened.

Patients with thyroid dysfunction, overt diabetes, arrhythmias, or those using drugs affecting heart rate or oral antidiabetic drugs were excluded. Prediabetic patients were identified based on fasting plasma glucose (FPG) values of 100–125 mg/dL and HbA1c of 5.7–6.4%, extracted from medical records. Patients with thyroid dysfunction, overt diabetes, arrhythmias, or those using drugs affecting heart rate were excluded.

All patients underwent 24-hour Holter ECG for some clinical indications, such as atypical chest pain, palpitations, or routine cardiovascular risk evaluation. Sampling was consecutive during the study period. Comparability between groups was ensured by matching for age and sex; baseline clinical variables were collected to assess potential confounding. HRV parameters—including SDNN, SDANN, rMSSD, pNN50, triangular index, and frequency-domain indices (LF, HF, VLF, LF/HF)—were calculated using validated software, after removing ectopic or artefact beats and ensuring $\geq 85\%$ analyzable NN intervals.

Approximately 150 files were reviewed, and only 25 prediabetic patients were selected. Exclusion criteria were strictly followed, and patients who did not meet the criteria were not included; therefore, the sample size remained limited.

When choosing the control group patients, patients with at least two different fasting blood glucose values below 100 mg/dl were included. All participants underwent 24-hour ambulatory ECG monitoring using a 5-lead Holter device (NorthEast Monitoring Inc. DR200 Holter Recorder) to evaluate heart rate variability. Recordings were analysed with the Northeast Holter Analysis System software automatically.

ECG recordings were reviewed, and artefacts and ectopic beats were automatically identified by the software and manually checked when necessary. Only normal-to-normal (NN) intervals were included in the HRV analysis. Recordings were considered valid if at least 85% of the total R–R intervals were suitable for analysis after artefact and ectopic beat correction.

Time-domain parameters included SDNN, SDANN, rMSSD, pNN50, and triangular index. Frequency-domain parameters included very low frequency (VLF: 0.0033–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), high frequency (HF: 0.15–0.40 Hz), and the LF/HF ratio. Frequency bands were defined according to standard international guidelines. The frequency bands are in accordance with the 1996 standards of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.

The primary HRV endpoint was predefined as rMSSD. This parameter was chosen because it is a reliable and reproducible indicator of short-term parasympathetic (vagal) activity and is commonly used in clinical studies evaluating autonomic function.

Secondary endpoints included time-domain parameters (SDANN, SDNN index, SDNN, and pNN50) and frequency-domain parameters (LF, HF, and LF/HF ratio).

Data distribution was assessed using normality tests. Variables with normal distribution were compared using Student's t-test, whereas non-normally distributed variables were analysed with the Mann-Whitney U test.

To minimise the risk of Type I error due to multiple comparisons, the Bonferroni correction was applied. As eight HRV parameters were evaluated, the adjusted level of statistical significance was set at $\alpha = 0.00625$.

Effect sizes were calculated to better interpret the magnitude of differences between groups. Cohen's d was used for parametric analyses, and $r (Z/\sqrt{N})$ was calculated for non-parametric analyses. Effect sizes were interpreted as small, medium, or large according to conventional thresholds (0.2, 0.5, 0.8 for Cohen's d; 0.1, 0.3, 0.5 for r).

Heart rate variability in the Holter ECG was interpreted, and it was investigated whether there was a statistical difference between the prediabetic patients and the control group.

The SPSS 22.0 package program was used for data analysis. Percentages and numbers for categorical variables, mean, standard deviation, median, minimum, and maximum values were calculated for numerical variables. The compliance of continuous numerical data with the normal distribution was evaluated visually with a histogram, statistically with Shapiro Wilk, Kolmogorov-Smirnov, Skewness, and Kurtosis tests. The Student t-test was used in the comparisons between two independent groups with normal distribution, the Mann-Whitney U test was used for two independent groups without normal distribution, p value was considered statistically significant at 0.05 and below.

Results

25 patients and 25 control groups were included in the study, which consists of 50 individuals in total. The patient and control groups were selected to be similar in terms of age and gender. (Table 4)

Table 4. Patient and control group characteristics

	Patient (n=25)	Control (n=25)
Age	56.2±9*	54.7±14*
Male	10	9
Women	15	16
HbA1c (%)	5.90±0.19*	-
FPG	106±4.33*	90.2±7.3*
Creatinine	1.23±1.51* mg/dL	0.81±0.14* mg/dL
TSH	1.66±0.85* uIU/mL	1.97±1.82* uIU/mL
sT4	1.00±0.13* ng/dL	0.98±5* ng/dL

HbA1c: Hemoglobin A1c, FPG: Fasting Plasma Glucose, TSH: Thyroid Stimulating Hormone, sT4: Serum Thyroxine (Free T4), *Mean±SD

Patients with fasting blood glucose values above 100 g/dl and HbA1c values between 5.7-6.4% were included in the study. None of the patients was using oral antidiabetic drugs, patients with heart failure, arrhythmia, using drugs that affect heart rate (β -blockers, etc.), patients with overt diabetes, patients with thyroid dysfunction, or patients with chronic kidney failure were excluded from the study.

The patient group consisted of 25 people, with an average age of 56.2, including 10 men and 15 women. The mean value of HbA1c was 5.9%. The average value of fasting blood glucose was found to be 106 mg/dl. In the patient group, the mean creatinine value was 1.23 mg/dL, the TSH value was 1.66 uIU/mL, and free T4 was 1 uIU/mL.

In the control group, the mean age was 54.7 years; 9 of the individuals in this group were men, and 16 were women. The mean fasting blood glucose value was 90.2 mg/dl. In the control group, the mean creatinine value was 0.81, the TSH value was 1.97 uIU/mL, and free T4 was 0.98 uIU/mL.

For Table 5, normality of each parameter was assessed using the Shapiro–Wilk test. Variables with normal distribution were analysed using Student’s t-test (mean \pm SD reported), non-normal variables using Mann–

Whitney U test (median [IQR] reported). For Table 6, normality of each variable was assessed using the Shapiro–Wilk test. Both the Triangle Index and VLF were normally distributed, Student’s t-test was used, and the results are presented as mean \pm SD. When we consider the heart rate variability parameters, it was seen that all parameters, the average of which was calculated, were lower in the patient group than in the control group. Among these values, the time parameters SDANN, rMSSD, pNN50 and Triangle index were statistically significant. Frequency parameters HF, VLF, and LF/HF were statistically significant. (Tables 5 and 6)

Table 5. Control and patient group heart rate variability parameters*

Parameter	Groups	N	Median	Mean \pm SD	Z	P value	Effect Size (95% CI)
SDANN	Control	25	116	140.56 \pm 60.95	-1.99	0.05	r=0.28(0.00–0.52)
	Patient	25	119	113 \pm 23.53			
SDNNi	Control	25	130	59.74 \pm 23.71	-1.7	0.09	r=0.24 (-0.04–0.49)
	Patient	25	126	57.52 \pm 34.38			
SDNN¹	Control	25	55	142.7 \pm 39.57	t:2.03	0.048	d=0.60 (0.03-1.16)
	Patient	25	51	123.11 \pm 20.5			
rMSSD	Control	25	31	34.67 \pm 19.43	-2.3	0.02	r=0.32 (0.04–0.55)
	Patient	25	23	26.81 \pm 11.97			
LF	Control	25	415	551.26 \pm 377.7	-0.86	0.38	r=0.12 (-0.16–0.39)
	Patient	25	460	469.54 \pm 344.5			
HF	Control	25	178	304.9 \pm 314.82	-2.26	0.02	r=0.32 (0.04–0.55)
	Patient	25	108	168.98 \pm 6.36			
LF/HF	Control	25	2,54	2.94 \pm 1.97	-0.58	0.50	r=0.08 (-0.20–0.35)
	Patient	25	3,46	3.61 \pm 1.93			
pNN50	Control	25	7	11.07 \pm 10.49	-2.09	0.04	r=0.29 (0.01–0.53)
	Patient	25	4	6.78 \pm 7.42			

SDANN: Standard Deviation of the Average NN intervals, SDNNi: Standard Deviation of NN intervals index, SDNN: Standard Deviation of NN intervals, rMSSD: Root Mean Square of Successive Differences, LF: Low-Frequency band, HF: High-Frequency band, LF/HF: Low Frequency to High Frequency ratio, pNN50: Percentage of NN50 intervals ¹:Student’s t-test, * Mann whitney U test

Table 6. Control and patient group heart rate variability parameters*

Parameter	Patient (n=25)	Control (n=25)	Statistic	P Value
Triangle I.	22.1±5.46	27.3±9.94	t:2.65	0.01
VLF (ms ²)	859.33±285.77	1115.29±415	t:2.47	0.02

*Student's t-test, Triangle I.: Triangular Index, VLF: Very Low Frequency band

Primary Endpoint

rMSSD was lower in the patient group compared with the control group (26.81±11.97 vs 34.67±19.43; p=0.02). The effect size was moderate (r=0.32; 95% CI: 0.04–0.55). However, after Bonferroni correction for multiple comparisons (adjusted $\alpha=0.00625$), this difference was no longer statistically significant.

Secondary Endpoints

SDNN values were lower in the patient group (p=0.048), with a moderate effect size (Cohen's d=0.60; 95% CI: 0.03–1.16).

HF was also reduced in patients (p=0.02), showing a moderate effect size (r=0.32; 95% CI: 0.04–0.55).

Similarly, pNN50 was lower in the patient group (p=0.04), with a small-to-moderate effect size (r=0.29; 95% CI: 0.01–0.53).

No statistically significant differences were observed for SDANN, SDNN index, LF, or LF/HF ratio. These parameters demonstrated small effect sizes (r<0.30).

After Bonferroni adjustment, none of the secondary endpoints remained statistically significant. Therefore, these results should be interpreted as exploratory.

Discussion

Autonomic neuropathy in diabetes is a complication that should be considered because of the cardiovascular effects it may cause. Previous studies suggest that autonomic neuropathy may develop in the early stages of diabetes, and some evidence indicates that similar alterations may also be present during the prediabetic stage. Our findings are consistent with the possibility that early alterations in cardiac autonomic regulation may already be present during the prediabetic stage. In our study, we found that autonomic neuropathy can start in prediabetic patients with high blood glucose and HbA1c but who do not fully meet the diagnostic criteria for diabetes.

Many previous studies have shown that cardiac autonomic neuropathy is common in diabetes and is generally associated with reduced heart rate variability.¹⁸

According to a study conducted by H Kudat et al.¹⁹ in 2006, heart rate variability parameters were found to be lower in diabetic patients compared to the control group. Similarly, in our study, all heart rate variability time and frequency parameters were found to be lower in the prediabetic group, which we defined as the patient group, compared to the control group.

In the study conducted by H Kudat et al. with 31 diabetic patients and 30 control groups, it was found that heart rate variability decreased in diabetic patients compared to the control group in a statistically significant manner in SDNN, SDANN, SD, pNN50, rMSSD, LF, HF, and Total Power parameters, except for Mean NN and LF/HF parameters.

In this study, which we conducted with 25 prediabetic patients and 25 control groups, the mean of heart rate variability parameters was found to be lower in the prediabetic group than in the control group in all parameters calculated. In our study, time parameters SDANN, rMSSD, pNN50 and Triangle index were statistically significant. Frequency parameters HF, VLF, and LF/HF were statistically significant. On the other hand, SDNN, SDNNi and LF parameters were not statistically significant, but the prediabetic group was lower than the control group. Due to certain limitations, the fact that the prediabetic patient sample was not numerically high was thought to affect statistical significance in all parameters.

In the study of Charlotte Coopmans et al.²⁰ published in *Diabetes Care* in 2020, the data of 550 prediabetic and 331 diabetic patients were examined, and heart rate variability time and frequency parameters were found to be lower than those of the population with normal glucose metabolism, and this decrease was found to be correlated with HbA1c and fasting blood glucose values in patient groups.

According to Fred Shaffer and JP Ginsberg, the SDNN parameter is one of the most important parameters evaluating cardiac risk and is one of the parameters that shows a decrease in cardiac autonomic neuropathy.²¹ The decrease in this parameter may be directly related to cardiac mortality. In our study, a mean decrease of approximately 20 ms in the mean SDNN values was found in the prediabetic group compared to the control group. Although there was no significant decrease, this decrease in heart rate variability in cardiac autonomic neuropathy caused by prediabetes is a warning for cardiovascular complications.

Again, according to Fred Shaffer and JP Ginsberg, it was stated that low rMSSD values may be associated with sudden cardiac death, and in our study, rMSSD values were found to be significantly lower in the prediabetic group compared to the control group. (prediabetic group: 26.81 ± 11.97 control group: 34.67 ± 19.43).²¹ This again shows that cardiac autonomic neuropathy, which may develop in prediabetes, is a complication that should be considered, and its early diagnosis is important.

In our study, the mean value of fasting blood sugar was found to be 106 mg/dl. In the patient group, the mean creatinine value was 1.23 uIU/mL, the TSH value was 1.66 uIU/mL, and free T4 was 1 uIU/mL.

The mean fasting blood glucose value was found to be 90.2 mg/dl. In the control group, the mean creatinine value was 0.81 mg/dL, the TSH value was 1.97 uIU/mL, and free T4 was 0.98 uIU/mL. There was no significant difference between the patient and control groups in terms of creatinine, TSH and T4 values. As expected, there was a significant difference between the means of fasting blood glucose values.

Heart rate variability measurement draws attention as a very popular, easily applicable noninvasive method that we can use to determine autonomic regulation of the heart and has direct prognostic value for cardiovascular risk.²²

Diabetes directly affects the cardiovascular system with its macro and microvascular complications and causes serious cardiovascular problems such as myocardial infarction, stroke, intermittent claudication, sudden death, arrhythmias, silent ischemia and heart failure.²⁰ Diabetes is also directly related to atherothrombosis and endothelial dysfunction.²⁰ In addition to all these effects, cardiac autonomic neuropathy is a condition that we are perhaps not very aware of the damage caused by diabetes in the cardiovascular system, which starts quietly but early, but needs to be cared for, recognised early and treated with the results it creates.

This study provides preliminary evidence that HRV parameters may be lower in prediabetic individuals compared to normoglycemic controls. All heart rate variability parameters were lower than those of the control group and can be considered as an indicator of cardiac autonomic neuropathy. No significant decrease was detected in some time and frequency parameters, which can be considered a limitation of our study, which was

caused by the small number of patients. These findings suggest that HRV may be reduced in prediabetes, consistent with possible early autonomic involvement.

Although several HRV parameters demonstrated moderate effect sizes suggestive of reduced vagal modulation in the patient group, statistical significance was attenuated after correction for multiple testing. These findings may indicate clinically relevant autonomic alterations; however, given the limited sample size and multiplicity adjustment, they should be interpreted as hypothesis-generating and require confirmation in adequately powered prospective studies.

It is possible to obtain more precise results in studies with similar large numbers of patients and multicenter studies. It is important and necessary to conduct new studies in the form of case-control with a larger number of patients on the subject to prove the onset of cardiac conotoma neuropathy in prediabetes.

Study Limitations

Heart rate variability is influenced by several metabolic and clinical factors, including hypertension, dyslipidemia, obesity, smoking status, and underlying cardiovascular comorbidities. Due to the retrospective design of the present study and limitations in available medical records, detailed data regarding these potential confounding variables were not consistently accessible. Therefore, adjustment for these factors could not be performed.

Ethical Considerations: The study was approved by the Non-Interventional Clinical Research Ethics Committee of the Faculty of Medicine, Ufuk University, with application date and number 20200703/16.

Conflict of Interest: The authors declare no conflict of interest.

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